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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/595,096	06/15/00	DILLER D	1073.060

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EXAMINER	
SHEINBERG, M	

ART UNIT	PAPER NUMBER
1631	3

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/595,096	Applicant(s) DILLER ET AL.	
	Examiner Monika B. Sheinberg	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☒ Claim(s) *10,20 and 30* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☒ The proposed drawing(s) filed on *15 June 2000* is: a)☒ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) 2 *2 sheets* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

It is to be noted that these claims can be grouped into three areas: method of the instant invention (claims 1-10), a system providing means to execute the method claimed (claims 11-20); and a machine readable storage medium that performs the execution of the method claimed (claims 21-30). Each claim in the first group directly correlates to its partner in latter two groups. For example, the method described in claim 1 correlates to the system of executing the method in claim 11, and correlates to the storage device of claim 22. Therefore statements concerning claims 1-10 are also directed to their sister claims 11-20 and 21-30 in accordance.

Claim Rejections - 35 USC § 112

The following is a quotation of the ***first paragraph*** of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 18, and 28, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPA 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1)

the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The mode of operation in claim 8 is not enabled in the instant application. The instant application lacks any amount or direction as to the practice of the mathematical equation of line 4. Nowhere in the claims or the specification is there a clear and direct explanation as to how and when the stated method is to be applied in the step of minimization. While working examples are not, per se, required, the specification must provide adequate guidance such that one of skill in the art could practice the invention without undue experimentation. Given the lack of working examples in the specification, and the unpredictability of the operation of minimization in the context of a complex protein, the specification, as filed is not enabling for the mathematical equation of minimization as claimed. As such, claims drawn to the operation of minimization of I(R, T) are not enabled. The operation of subtracting a vector that holds a value and direction (T), from the "hot spot" of a protein, is not enabled; just as the operation of multiplication an atom (A_j) and a matrix that is defined by coordinates is not enabled.

Claims 10, 20, and 30, are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The BFGS optimization algorithm of the stated claims is critical or essential to the practice of the invention, but is not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPA 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The instant application lacks any amount or direction as to the practice of the BFGS optimization method. Nowhere in the claims or the specification is there a clear and direct explanation as to how and when the stated method is to be applied in a key step of optimization of ligand positioning. This critical amount of information pertaining to directing one skilled in the art to perform the practice of the present invention is lacking, thus causing undue experimentation. As essential to the practice of the invention, the BFGS method cannot be referenced to a printed publication by the specification as on page 12, lines 13-18. That which is particular to the practice of the present invention must be selected out the referenced text and included the instant application.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner

representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The following is a quotation of the ***second paragraph*** of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 6, 8-10, 14, 16, 18-20, 24, 26, and 28-30, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 (14 and 24) is rejected, as having unclear language that causes a confusing conflict as to what is the desired meaning. In line 3, the term "randomly" contradicts the following term "uniformly". If the conformations gathered are uniform in distribution they cannot be a result of a random generation. Claim 4 also fails to define what constitutes the apex of the "top cluster" (line 11).

Claim 8 (18 and 28) is rejected for lack of clarity as to what the equation provided in line 4 is "minimizing". The minimization of an unknown quality not defined in either the claims or the specification renders the claim indefinite.

In addition, claim 8 is rejected due to the confusion caused by a lack of clearly defined values that are set forth in lines 6-10. The operation of subtracting a vector that holds a value and direction (T), from the "hot spot" of a protein, is unclear; just as the operation of multiplication an atom (A_j) and a matrix that is defined by coordinates is unclear.

Claims 6, 9, and 10 (16, 19, 20, 26, 29, and 30), are rejected as having broad claims that do not represent the narrow limitations of the scoring methodology that are presented within the specification. Claim 6 states a broad selection of "best scores" (line 11), yet does not provided the parameters that define a best score. Thus it is unclear as to what is best. Claim 9 describes the ranking of ligand positions based on a derived score that also lacks parameters (lines 7-8). The same lack of limitations as described in claim 9, pertain to claim 10, line 4. Given that the parameters were not provided in the claims, the terminology of ranking and scoring is left to subjective rendering. Since the resulting claims do not clearly set forth the metes and bounds of the patent protection desired, they are rendered indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 9, 11-17, 19, 21-27, and 29, are rejected under 35 U.S.C. 102(b) based upon anticipation of the invention, by Ho et al. (Pro. of 27th Hawaii Int'l Conf. on System Science, 1994).

Ho et al. anticipates the instant invention in each method, system, and storage, by his drug-design system that consists of four programs that are integrated to design ligands by their docking with rigid proteins: CAVITY, FOUNDATION, DBMAKER, and SPLICE.

The CAVITY software teaches on page 215 (1st column, top paragraph) the solid three-dimensional model casting protein active sites to allow "uninterrupted ligand manipulation and modification". Thus CAVITY demonstrates the visualization of the "hot spots" (or active sites) of a fixed target protein that allow the translation, orientation and rotation of a flexible ligand as described in claim 1, lines 5-15. The CAVITY also demonstrates the utilization of hydrogen bonding sites for the characterization of "optimal interaction sites" (pg. 215, 1st column) which is described in claims 5 (line 6)as well as inherently taking into account polar or apolar atom type.

The FOUNDATION software teaches on page 215 (2nd column, 1st paragraph), a three-dimensional database search and retrieval program that uniquely generates and stores a set of multiple ligand solutions as described in claims 1 (lines 3-4), 2 (lines 2-3), and 3 (2-3). A search query of this database generates "preferred" ligands that "more effectively complement the target receptor" (pg. 216, 1st column, 3rd paragraph); thus describing a ranking or scoring of the ligands as in claims 6 and 9. The FOUNDATION also describes on page 216 (1st column, 4th and 5th paragraphs) the transformation of ligand structures that match (claim 7, lines7-8) specified configurations and their docking, or placement (claim 7, line10), into the active site in its "appropriate orientation" (pg. 216, 1st column, 3rd to last line). The "FOUNDATION + 3D databases" in Figure 1 (pg. 219), Ho et al. demonstrates the use of pharmacophoric elements in a specified exact 3D geometry to search 3D databases, thus describes the "grid-like search" of claim 6, line 7. Given that the FOUNDATION software preferably selects ligand structures "which more effectively complement the target receptor" (pg. 216, 1st column, 3rd paragraph), Ho et al. demonstrates a mode of ranking the conformations as described in claim 9.

The DBMAKER software (with CONCORD) teaches on page 215 (2nd column, 3rd paragraph) a personalized three-dimensional database that allows the generation of "random

compounds within the scope" (pg. 215, 2nd column, 3rd paragraph) of user-defined constraints of a "pre-docking conformational search" as described in claim 4.

The SPLICE software teaches an editing module to "ensure the steric compatibility" (pg. 216, 2nd column, 2nd paragraph) of the generated ligand-protein complexes. Thus SPLICE describes the binding optimization in claims 1 (line 12); the "rigid body" use in optimization of claim 7 (line 7); and the elimination of steric clash of claim 9 (lines 4-6), which is reasonably interpretable as minimizing conformational strain. The consideration of ligand translation, orientation, and rotation, of claims 1 (lines 13-14) and 9 (lines 12-13), are inherent of the process of elimination of steric clash and compensation of "atomic motion" (pg. 216, 2nd column, 3rd paragraph).

Each program of the reference is a different system and software that teach the systems claims 11-17 and 19, and the storage mediums of claims 21-27, and 29. For example, page 217 (1st column, 2nd paragraph) demonstrates a storage medium, files, that store molecular information from their EDIT module.

Claim Objections

Claims 10, 20, and 30, are objected to because of the following informalities: the full name of the BFGS optimization algorithm must be provided before the acronym is used. Appropriate correction is required.

No claim is allowed

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located

in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242, or (703) 308-4028.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Monika B. Sheinberg, whose telephone number is (703) 306-0511. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst, Tina Plunkett, whose telephone number is (703) 305-3524, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

May 14, 2001

Monika B. Sheinberg
Patent Examiner
Art Unit 1631

ARDIN H. MARSCHEL
PRIMARY EXAMINER